respectfully requested.

At page 2 of the Official Action, the Examiner has acknowledged Applicants' election of Invention II, Claims 2-5 and 19. Claims 1 and 6-18 have been canceled.

The Examiner also objected to the abstract of the disclosure and requests that the abstract be amended to reflect the elected invention. The abstract has been amended in accordance with the present amendment to reflect that the invention comprises a method of detecting *Aspergillus* species.

At page 3 of the Official Action, the Examiner has rejected Claims 2-5 and 19 under 35 U.S.C. §112, second paragraph, as allegedly indefinite for failing to particularly point out and distinctly claim the subject matter regarded as the invention. Claims 2-5 have been amended. Claim 19 has been canceled and new Claims 20-22 have been added. The foregoing amendments and new claims place the claims in compliance with the requirements of 35 U.S.C. §112, second paragraph.

At page 7 of the Official Action, the Examiner has rejected Claims 2-4 and 19 under 35 U.S.C. §103(a) as allegedly unpatentable over White et al. (PCR Protocols, 1990) and Beck (U.S. Patent No. 5,827,695) in view of Borsuk et al. (Acta Biochimica Polionica, 1994), Nikkuni et al. (J. Gen. Appl. Microbiol., 1998), Pazoutova (Genbank Accession Number AJ001331), Peterson (Genbank Accession Number U65306) and Aguirre et al. (Genbank Accession Number U93683).
Claim 5 has also been rejected under 35 U.S.C. §103(a) as allegedly unpatentable over the references listed above in further view of Nelson et al. (U.S. Patent No. 5,827,656).

In view of the amendments presented herewith and the remarks that follow, Applicants respectfully submit that the claims are in condition for allowance. Accordingly, early and favorable action on this application is earnestly solicited.

CLAIMS 2-5 AND NEWLY ADDED CLAIMS 20-24 FULLY COMPLY WITH THE REQUIREMENTS OF 35 U.S.C. §112, SECOND PARAGRAPH

The Examiner has rejected Claims 2-5 and 19 under 35 U.S.C. §112, second paragraph, as allegedly indefinite for failing to particularly point out and distinctly claim the subject matter regarded as the invention.

The relevant inquiry in determining whether a given claim satisfies the requirements of 35 U.S.C. §112, second paragraph, is whether the claim sets out and circumscribes a particular area with a reasonable degree of precision and particularity such that the metes and bounds of the claimed invention are reasonably clear. In re Moore, 169 U.S.P.Q. 236 (C.C.P.A. 1971). Applicants respectfully submit that with respect to Claims 2-5 and new claim 20-22 this inquiry must be answered in the affirmative.

Claims 2-5 and 19 are allegedly indefinite for the following reasons:

1) The Examiner finds the term "known" in claims 2-5 unclear;
2) Claim 2 contains a typographical error;
3) The term "being" in claims 2-5 allegedly fails to convey the metes and bounds of the claims;
4) The recitation "using one or more detectably labeled probes directed to a portion of the hypervariable region bracketed by said primers, each said labeled probe being specific for one of the said fungal species from said group to determine whther said fungal species identified by each said labeled probe is present in said sample" in claims 2-5, followed by the language in claim 4 allegedly renders this claims set indefinite as the Examiner is unclear as to the metes and bounds of the claims.
5) Claims 3-5 improperly depend from claim 1, a product claim;
6) The Examiner contends that claim 19 is indefinite as it appears to be directed to five different methods.

In response to the foregoing rejections the claims have

been amended as follows:

1) The term "known" has been omitted from claims 2-5;

2) The misspelling of the term "oligonucleotide" in step b) of claim 2 has been corrected;

3) The word "being" in claim 2 has been replaced with the phrase "consisting of";

4) Claims 2-5 have been amended to recite the primer set of the invention which amplify the specified region of the fungal genome following by probing with specific SEQ ID NOS. 3-8;

5) Claims 3-5 have been amended such that they now depend from claim 2;

6) Claim 19 has been canceled and new claims 20-22 added which particularly set forth the method steps required to detect a nucleic acid sequence associated with a particular *Aspergillus* infection utilizing the different methodology encompassed by original claim 19.

In connection with the Examiner's uncertainty with reference to the relationship between claims 2 and 4, claim 2 has been amended to recite that the amplified nucleic acid sequence is probed with at least 15-25 nucleotides of a sequence selected from SEQ ID NO: 3-8 which distinguish the species from another. Support for this amendment can be found at page 10 and in Addendum 1 of the specification. Applicants respectfully submit that one of ordinary skill in the art, having the instant specification before them could readily determine the appropriate hybridization conditions without undue experimentation. As an additional matter, while the specification does disclose that probes are preferably between 15-25 nucleotides in length, one of ordinary skill in the art appreciates that probes may be approximately 600 nucleotides in length as well. Accordingly, Applicants submit that the claims satisfy the requirements of 35 U.S.C. §112, second paragraph.

In light of the present claim amendments, Applicants respectfully submit that Claims 2-5 and newly added Claims 20-

22 are not indefinite and request that the rejection of the claims under 35 U.S.C. §112, second paragraph, be withdrawn.

CLAIMS 2-5 AS AMENDED AND NEW CLAIMS 20-24 ARE PATENTABLY DISTINCT OVER THE CITED PRIOR ART

Claims 2-4 and 19 have been rejected under 35 U.S.C. §103(a) as allegedly unpatentable over White et al. (PCR Protocols, 1990) and Beck (U.S. Patent No. 5,827,695) in view of Borsuk et al. (Acta Biochimica Polionica, 1994), Nikkuni et al. (J. Gen. Appl. Microbiol., 1998), Pazoutova (Genbank Accession Number AJ001331), Peterson (Genbank Accession Number U65306) and Aguirre et al. (Genbank Accession Number U93683). Claim 5 has also been rejected under 35 U.S.C. §103(a) based of the references listed above and further in further view of Nelson et al. (U.S. Patent No. 5,827,656).

The Examiner takes the position that White et al. teach that IST1 and ITS5 are located within the small rDNA and ITS4 is located in the larger rDNA which would allow amplification of both the ITS1 and ITS2 regions which are highly variable among species. The Examiner further contends that Beck teaches that methods to clone ITS DNA sequences are known in the art as well as the general isolation of DNA from fungal isolates. The Examiner acknowledges that neither White et al. nor Beck teach SEQ ID NO: 2. Applicants note that Beck is directed to an analysis of fungal pathogens of wheat rather than medically important *Aspergillus* species.

The Examiner states that Borsuk et al. show alignments of ITS1 and ITS2 regions of three *Aspergillus* species. Applicants note that Borsuk et al. also do not disclose a sequence of SEQ ID NO: 2.

The Examiner relies in Nikkuni et al. for the teaching that ITS regions may be used to distinguish between strains of fungi.

The Examiner cites Pazotova et al., Peterson et al. and Aguirre et al. for teaching *Aspergillus* sequences from

Aspergillus terreus, *Aspergillus niger* and *Aspergillus fumigatus* respectively. Each of these sequences contains, but does not disclose, an isolated primer sequence of SEQ ID NO: 2.

According to the Examiner, it would have been *prima facie* obvious to one of ordinary skill in the art to modify the teachings of White and Beck given the specific sequences for *Aspergillus* as taught by Borsuk, Nikkuni, Pazoutova, Peterson and Aguirre. Applicants respectfully disagree.

The relevant inquiry in determining obviousness under 35 U.S.C. §103 based on the combined disclosure of references, is whether the references supply some teaching or suggestion to one of ordinary skill in the art to arrive at the invention as claimed. In re Dow Chemical Company, 5 U.S.P.Q.2d 1529 (Fed. Cir. 1988). Obviousness cannot be established by combining the teachings of the prior art to produce the claimed invention, absent some teaching or suggestion supporting the combination. In re Fine, 5 U.S.P.Q.2d 1596 (Fed. Cir. 1988). Moreover, the teaching or suggestion supporting the desirability or the combination must be found in the prior art, not in the applicant's disclosure. In re Fritch, 23 U.S.P.Q.2d 1780 (Fed. Cir. 1992). Under these standards, none of the cited references, considered singly or in combination, renders obvious the invention as presently claimed in claims 2-5 and 19.

Claim 2 has been amended to recite a method to identify pathogenic Aspergillus species from a patient sample in order to determine whether the patient has an *Aspergillus* infection. The method further entails identifying the particular species of *Aspergillus* causing the underlying infection. Support for this amendment can be found at page 29, lines 23-30.

The prior art references cited by the Examiner do not suggest all of the features of the methods provided in Claims 2-5. Specifically, none suggest the use of the instant method for identifying pathogenic fungi in clinical samples obtained

from patients suspected of having an *Aspergillus* infection. Applicants also note that SEQ ID NO:2 is not disclosed in any of the cited references. The Examiner's assertion that SEQ ID NO: 2 is a structural homolog of the ITS4 sequence of White et al. flies in the face of the patent office position that each nucleic acid sequence is a separate and distinct invention. There is nothing whatsoever structurally homologous between the ITS4 sequence of White and SEQ ID NO: 2.

The Examiner is relying on disclosure of full length sequences that include, but do not teach, or suggest SEQ ID NO: 2. Moreover, nowhere in any of the cited references is there a suggestion or teaching to combine the references to devise a method for specifically identifying various pathogenic Aspergillus species in a biological sample using the probes of SEQ ID NOS: 3-8. It is a well-settled premise in patent law that "Silence in a reference is not a proper substitute for adequate disclosure of facts from which a conclusion of obviousness may justifiably follow". In re Burt, 148 U.S.P.Q. 548 (CCPA 1966).

The Examiner acknowledges that the primer set of the instant claims were modified (and thus are distinct from the prior art primers) to optimize the amplification procedure and cites *In re Aller* for the premise "that when general conditions of a claim are disclosed in the prior art it is not inventive to discover optimum or workable ranges by routine experimentation". Applicants primer set is unique. Thus, *In re Aller* is not applicable to the facts of the instant case as Applicants are not merely working to discover optimum or workable ranges of known compositions.

The Examiner has further rejected claim 5 under 35 U.S.C. §103(a) over White et al. and Beck, in view of Borsuk et al., Nikkuni et al., Pazoutova, Peterson, Aguirre and further in view of Nelson et al. The deficiencies of the references cited in connection with the rejection of claims 2-4 and 19 under §103(a) have been set forth above. The disclosure in US

Patent 5,827,656 fail to make up for these deficiencies to render claim 5 obvious.

In light of all the foregoing, Applicants respectfully submit that Claims 2-5 as amended and new Claims 20-22 are not obvious in view of the cited prior art and request that the rejection of Claims 2-5 and 19 under 35 U.S.C. §103(a) be withdrawn.

In view of the amendments and remarks presented herein, it is respectfully urged that the rejections set forth in the October 19, 2001 Official Action be withdrawn and that this application be passed to issue. In the event the Examiner is not persuaded as to the allowability of any claim, and it appears that any outstanding issues may be resolved through a telephone interview, the Examiner is requested to telephone the undersigned attorney at the phone number given below.

Respectfully submitted,

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Enclosures: Appendix A

Appendix A

In The Specification:

(Page 52, line 2) Materials and methods are provided which rapidly and specifically differentiate between pathogenic and non-pathogenic [fungi] *Aspergillus* species in a biological sample.

In The Claims:

2. (Amended) A method of determining whether one or more fungal *Aspergillus* species selected from the group [of fungal species] consisting of *Aspergillus ustus* (SEQ ID NO: 3), *Aspergillus terreus* (SEQ ID NO 4), *Aspergillus niger* (SEQ ID NO: 5), *Aspergillus nidulans* (SEQ ID NO: 6) *Aspergillus fumigatus* (SEQ ID NO: 7), and *Aspergillus flavus* (SEQ ID NO: 8), [*Pseudallescheria boydii, Fusarium solani, Fusarium oxysporum, Fusarium monilliformes, Penicillium spp., Malassezia furfur, Malbarnchia spp., Cylindrocarpon lichenicola, Cladophialophora bantiana, Arthrogrothilus spp., Gymnascella hyalinaspora, Cylindrocarpon destructans, Sporothrix schenkii, Blastomyces dermatitides, Penicillium marnefeii, Histoplasma duboisii, Histoplasma capsulatum, Coccidiodes immitis, Cryptococcus neoformans, Issatchenkia orientalis, Candida albicans, Candida tropicalis, Candida lusitaniae, Candida glabrata, and Candida parapsilosis*], is present in a sample, said method comprising the following steps:

a) extracting nucleic acid material from fungi contained in [said] a patient sample from a patient suspected of having an *Aspergillus* infection;

b) adding two [known oligonucleocide] oligonucleotide primers, one of said primers [being] consisting of [()]SEQ ID NO:1[()] and the other primer [being] consisting of [()]SEQ ID NO:2[()], said primers bracketing a

hypervariable region on the rRNA present in the fungal species of said group;

c) amplifying the sequence between said primers; and

d) using one or more detectably labeled probes directed to a portion of the hypervariable region bracketed by said primers , said probes being selected from the group consisting of at least 15-25 contiguous nucleotides of SEQ ID NO: 3, SEQ ID NO: 4, SEQ ID NO: 5, SEQ ID NO: 6, SEQ ID NO: 7 and SEQ ID NO: 8 which distinguish said species, each said labeled probe being specific for one of said fungal species from said group, to determine whether said fungal species identified by each said labeled probe is present in said sample.

3. (Amended) The method of claim [1] 2 [in which, in said amplifying step,] wherein said amplifying procedure is the polymerase chain reaction.

4. (Amended) The method of claim [1] 2 in which said one or more probes hybridize to a nucleic acid sequence encoding the internal spacer regions of a pathogenic *Aspergillus* species gene sequence and is selected from the group consisting of (SEQ ID NO:3), (SEQ ID NO:4), (SEQ ID NO:5), (SEQ ID NO:6), (SEQ ID NO:7), and (SEQ ID NO:8)[, (SEQ ID NO:9), (SEQ ID NO:10), (SEQ ID NO:11), (SEQ ID NO:12), (SEQ ID NO:13), (SEQ ID NO:14), (SEQ ID NO:15), (SEQ ID NO:16), (SEQ ID NO:17), (SEQ ID NO:18), (SEQ ID NO:19), (SEQ ID NO:20), (SEQ ID NO:21), (SEQ ID NO:22) and (SEQ ID NO:23), (SEQ ID NO: 24),(SEQ ID NO:25),(SEQ ID NO:26),(SEQ ID NO:27),(SEQ ID NO:28), (SEQ ID NO:29),(SEQ ID NO:30), and (SEQ ID NO:31), (SEQ ID NO:32), (SEQ ID NO:33)].

5. (Amended) The method of claim [1] 2 wherein, in step (d), more than one probe is used, each said probe being connected to (a) a different signal moiety or (b) a moiety

which allows separation of said probes.